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**THERMAL REGULATORY RESPONSES OF UNANESTHETIZED
DOGS DURING HYPOTHALAMIC TEMPERATURE
MEASUREMENT AND STIMULATION**

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SEPTEMBER 1961

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**BIOMEDICAL LABORATORY
AEROSPACE MEDICAL LABORATORY
AERONAUTICAL SYSTEMS DIVISION
AIR FORCE SYSTEMS COMMAND
UNITED STATES AIR FORCE
WRIGHT-PATTERSON AIR FORCE BASE, OHIO**

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CONTRACT MONITOR: ABBOTT T. KISSEN, PH.D.
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FOREWORD

The studies in thermal regulatory responses of unanesthetized dogs during hypothalamic temperature measurement and stimulation presented in this report were conducted between January 1960 and June 1961, in the Department of Physiology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. The research was performed under provisions of Contract AF 33(616)-6306, for the Aerospace Medical Laboratory, in support of Project 7163, Physiology Research, and Task 71820, Studies of Mechanism of Mammalian Thermal Regulation; Dr. A. T. Kissen, Biothermal Section, Biophysics Branch of the Biomedical Laboratory, was the contract monitor for Aerospace Medical Laboratory. These studies were also supported by Research Grant B-1508 with the U. S. Public Health Service.

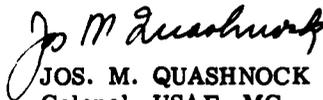
Animal experimentation was performed in accordance with the Rules for Animal Care as established by the American Medical Association.

ABSTRACT

The role of the hypothalamic and skin temperatures in controlling thermal response of a resting dog was studied by two methods: (1) measurements were made of hypothalamic, rectal, ear skin, and trunk skin temperatures of the dog in winter fur in hot, neutral, and cold environments; respiration rate and shivering were observed: (2) a thermal clamp (six thermodes surrounding the hypothalamus and perfused with water to hold it at approximately 38.7° C) was used to measure thermal and metabolic responses of the resting, fasting dog during exposure to a wide range of temperatures. Although skin and hypothalamic temperatures were found to contribute to shivering and panting, a relationship between the hypothalamic and skin temperatures and the motor responses could not be established.

The mode and site of pyrogenic action were established by the following methods. Assuming that these agents act on the thermally sensitive cells of the anterior hypothalamus by raising the set point for physiological temperature regulation to a higher level, we planned to either counteract their effect by heating this region of the hypothalamus with 3.7 megacycle radio frequency energy between implanted thermodes, or enhance their effect by cooling the area by circulating water through the thermodes. The hypothalamus was heated (1) immediately after pyrogen was administered, (2) while fever developed, and (3) during maximum fever. In the first case, fever did not develop, in the second, rise in rectal temperature was stopped, and in the third, thermoregulatory responses were similar to those obtained using the same technique at normal body temperature. A hyperfever was produced when pyrogenic action was enhanced by hypothalamic cooling.

PUBLICATION REVIEW



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INTRODUCTION

When imposing an external thermal stress upon a homiothermic animal it is difficult to determine whether the heat conserving or heat dissipating responses of the animal are due to thermal receptors located in the periphery or in the core of the animal or due to some combination of these two. Although careful measurements of the motor responses of an animal to its thermal environment are important, they do not serve to answer questions concerning the internal thermal drives or the type of controller involved in temperature regulation. The objectives of the studies upon which this report is made were: I. - to obtain a quantitative relationship between the hypothalamic and skin temperatures and the motor responses of a resting dog in a neutral, cold, and hot environment (ref. 1) and II. - to observe the effect of a controlled displacement of the hypothalamic temperature upon the development of fever (ref. 2).

The role of the hypothalamic and skin temperatures in controlling the thermal response of a resting dog was studied by two methods. A. Many measurements of hypothalamic, rectal, ear skin and trunk skin temperatures were made on the resting, fasting dog in its winter fur in hot, neutral, and cold environments while observations of respiration rate, shivering and body position were made. B. A "thermal clamp" was placed on the hypothalamus to hold it at approximately 38.7°C while the thermal and metabolic responses of the resting, fasting dog were measured when exposed to a wide range of environmental temperatures. The response of such an animal may be attributed to the extra-hypothalamic thermal receptors. Subsequently, any increment of response that followed upon removal of the thermal clamp may be attributed to the hypothalamic receptors.

I. Relationship Between Hypothalamic and Skin Temperatures and the Thermal Regulatory Responses of the Resting Dog Exposed to Hot, Neutral, and Cold Environments. H. T. Hammel, D. C. Jackson, and J. D. Hardy.

METHOD

Thermodes were implanted around the hypothalamus of mongrel dogs. The thermodes served both for measurement of the hypothalamic temperature by inserting a thermocouple to the bottom of the thermode and for thermal stimulation of the hypothalamus by perfusing the thermodes with water. Two rows of thermodes, each 4 mm from the midline, were passed through short sleeve guides driven through the skin and skull when the animal was under general anesthesia and head was held in a stereotaxic instrument, Figure 1 (ref. 3 and 4). The sleeve guides were placed in each row at 19, 22, 25 and 28 mm anterior to the ear bars. The anterior commissure in the dog is approximately 25 mm anterior to the ear bars. Several weeks after preparation thermocouples were inserted into selected thermodes or the three anterior pairs were perfused with

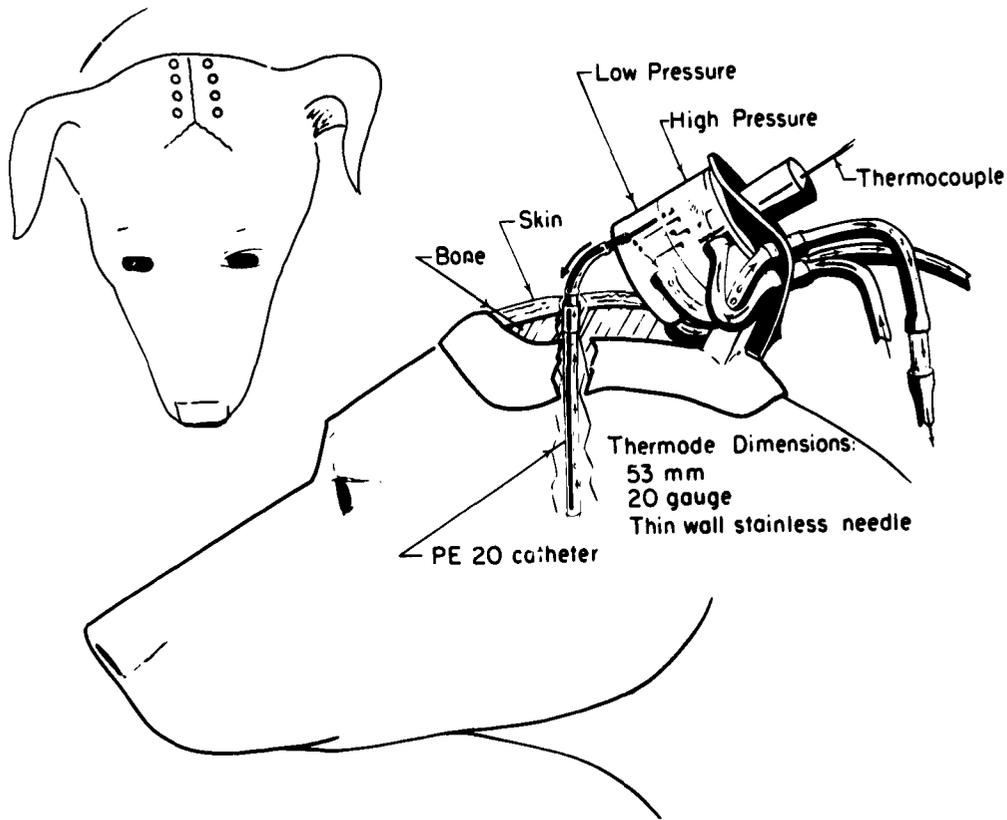


Fig. 1 Details of thermode and head circulator. Positions 1 through 6 on insert were 31, 28, 25, 22, 19, and 16 mm, respectively, anterior to the ear bars of the stereotaxic instrument.

water from the circulator mounted above the head (figure 1) and a thermocouple was placed in one of the posterior pair of thermodes. When thermal stimulation of the hypothalamus was required, water from a constant temperature bath was circulated through the upper chamber of the head circulator at a high rate. The bath temperature was held constant ($\pm 0.05^{\circ}\text{C}$) with a Doelcam controller Model 2 HCR-1, and the temperature could be quickly adjusted to any desired temperature between 30°C and 45°C by the addition of cold or hot water. The temperature of the water passing through the head circulator was continuously recorded with a thermocouple inserted in the upper chamber. Water from the upper chamber of the head circulator flowed to the tip of the thermode when the lower chamber was connected to a vacuum line.

The dog was trained to rest quietly on a platform in an air conditioned box, 35" x 29" x 29". Forced air entered the chamber through a 6 inch

port in the top of the box above the dog. A baffle in front of the port prevented air from striking the dog directly. Air left the chamber through a 6 inch port low on one end of the chamber. The temperature of the box could be held constant at temperatures between 10°C and 45°C and rapid transitions could be made from one temperature to another.

Continuous recordings of oxygen consumption, evaporative heat loss from the mouth, rectal temperature, hypothalamic temperature, the average of 8 to 10 skin temperatures, the skin temperatures of the ear and trunk, air temperature and temperature of stimulating water were made as shown in Figure 2. The dog was trained to wear a clear plastic hood over its head for metabolic measurements.

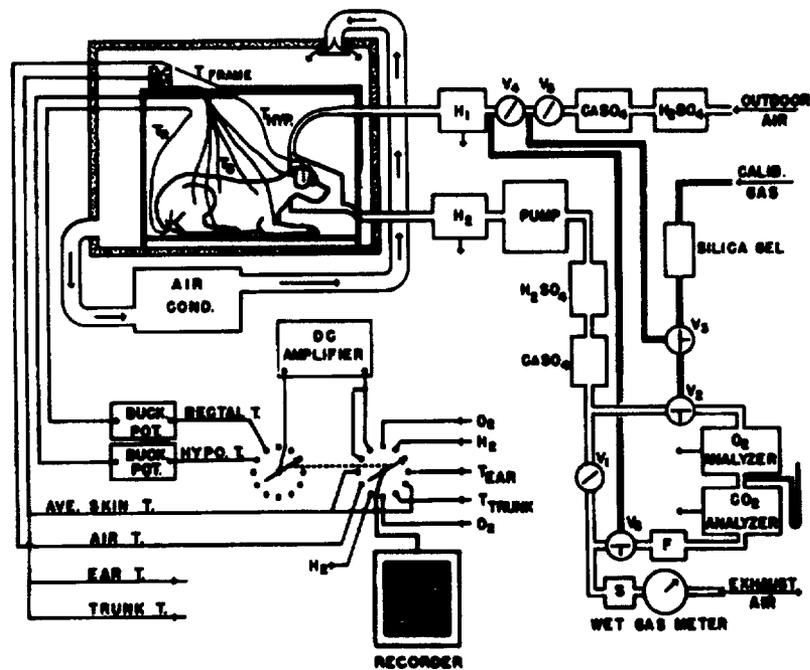


Fig. 2 System for recording oxygen consumption, evaporative heat loss from mouth, rectal, skin and hypothalamic temperatures, air temperature and temperature of stimulating water in head circulator.

RESULTS

A. Hypothalamic, Rectal, Ear Skin and Trunk Skin Temperatures on Resting Dog Exposed to Hot, Neutral, and Cold Environments.

Temperatures and notes on respiration rate and shivering are recorded in Figures 3, 4, and 5 for three runs on separate days on the same dog. The dog still had its winter underfur although living in heated animal quarters for two months. In the convective environment within the animal chamber, the neutral dry bulb temperature for this dog was about 25°C or 2 to 3°C below the neutral temperature for a dog without a winter coat of fur. For the first thirty-three minutes of the record in Figure 3, the dog rests quietly at 27°C. (Note that the record runs from right to left and that the lower record is a continuation of the upper record.) The high ear temperature indicates that the animal was vasodilated. The air temperature was raised to 35°C which shortly thereafter initi-

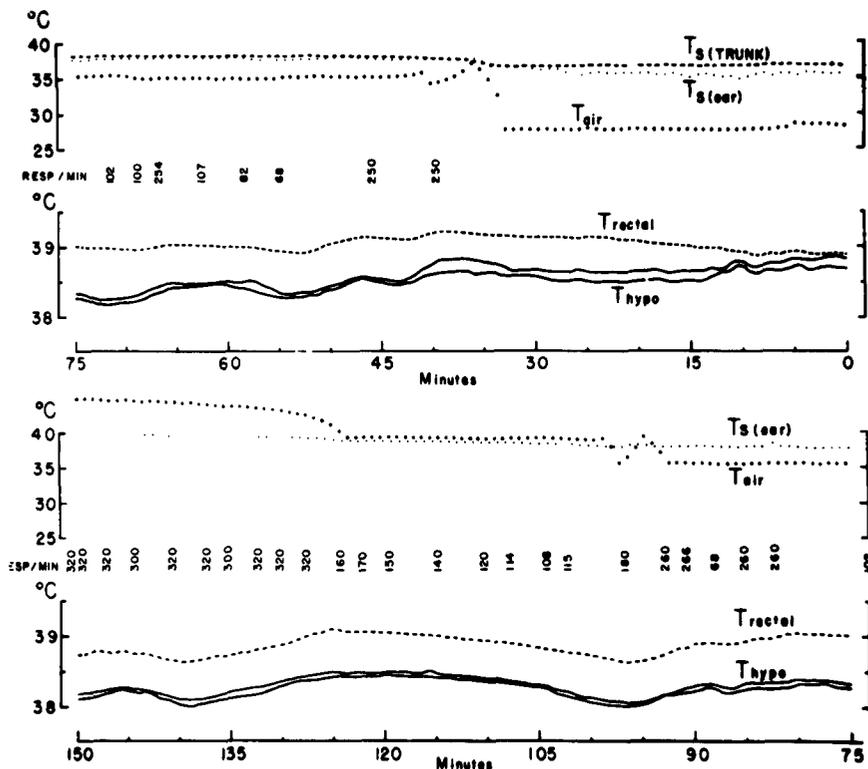


Fig. 3. Body temperatures of resting, fasting dog with winter fur exposed to warm and hot environments. T_s (trunk) - skin temperature of trunk; T_s (ear) - skin temperature of ear; T_{rectal} - rectal temperature; T_{hypo} - hypothalamic temperatures at A- 25 mm and 4 mm to the left and 4 mm to the right of midline; T_{air} - air temperature.

ated panting. For respiration rates in excess of 250 breaths per minute, the dog was able to lower its hypothalamic and rectal temperatures. At an air temperature above 45°C the dog, by panting, dropped its hypothalamic temperature from 38.5°C down to 38.1°C . Both hypothalamic temperatures in Figure 3 were recorded at the level of and below the anterior commissure.

In Figure 4a the dog was again started off in a warm environment of 27°C . Here is illustrated an event seen repeatedly in animals in neutral or warm environments (but not in cold). When the head was down, the hypothalamic temperature was always lower than when the head was held up. The difference may be as much as 0.5°C and a decreasing temperature never elicits shivering nor does an increasing temperature elicit panting. The changes in temperature could be explained by difference in the rate of perfusion of the brain stem (ref. 5).

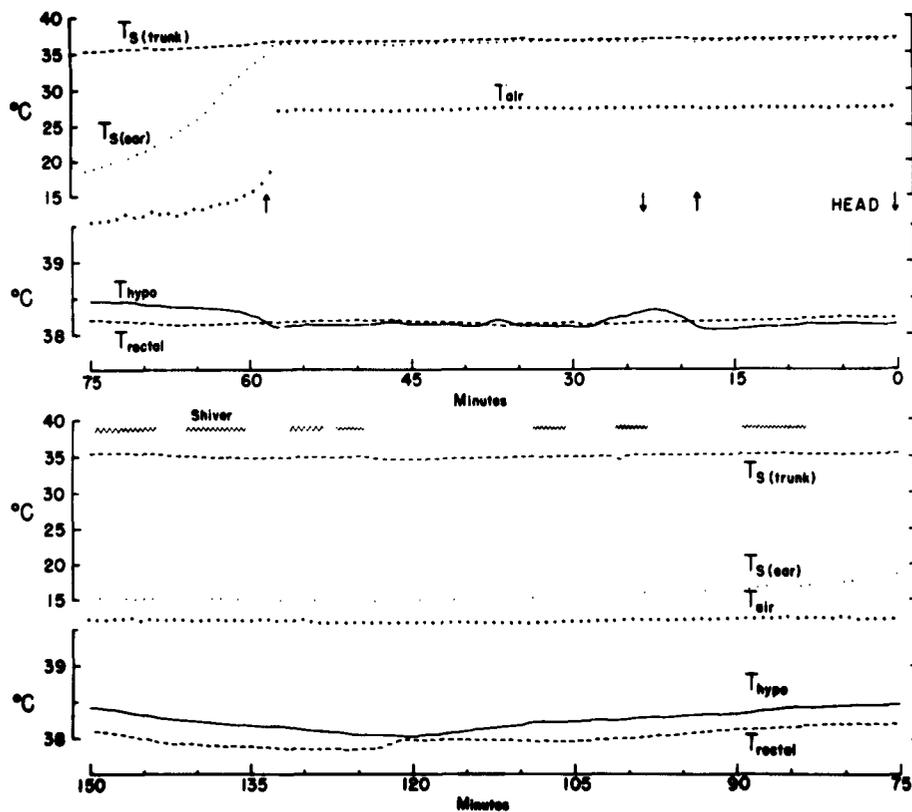


Fig. 4a Body temperatures of same dog as Fig. 3 resting and fasting exposed to neutral, cold, and hot environments.

When the head was elevated, the perfusion pressure of the brain decreased by the amount of hydrostatic pressure of the column of blood from heart to head causing the blood flow to decrease so that the brain stem was cooled less.

At 58 minutes in Figure 4a the air temperature was dropped from 27°C to 10°C. Within 30 minutes, traces of shivering occurred at a hypothalamic temperature of 38.5°C. The shivering was not vigorous enough to prevent a decline to 38.1°C. Note that in Figure 3 the animal was panting at no higher hypothalamic temperatures than these. The animal can shiver enough to regain hypothalamic temperature, as seen at 120 to 150 minutes in Figure 4a.

Figure 4b is a continuation of Figure 4a. At 167 minutes the air temperature was increased to 45°C. The hypothalamic temperature passively increased to 38.6°C with no panting. 45 minutes later the dog was panting vigorously although the hypothalamic temperature was down 1/10°C to 38.5°C. Note, this is no higher than it was when the animal was shivering vigorously and also it is 0.4 to 0.5°C higher than it was in Figure 3 when the same dog was panting no less vigorously and had no higher skin temperature.

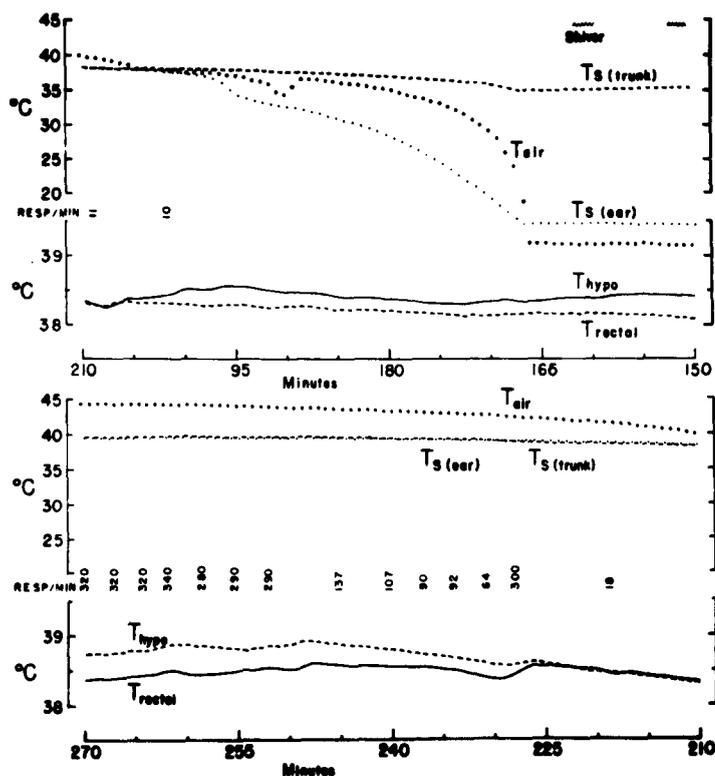


Fig. 4b Body temperatures of same dog as Fig. 3 resting and fasting exposed to neutral, cold and hot environments.

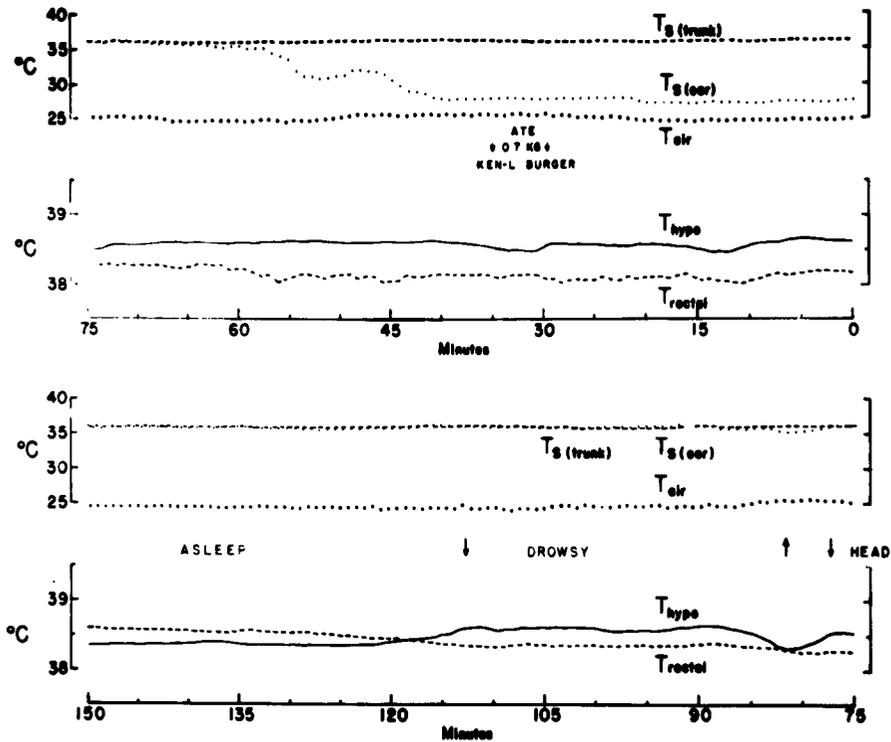


Fig. 5 Body temperatures of same dog as Figure 3 resting and feeding exposed to neutral environment.

Figure 5 is another record on the dog maintained at 25°C throughout the run. After a long quiet period, the animal was fed 0.7 Kg of Ken-L Burger. Before feeding, the ear skin temperature was only a few degrees above ambient thus indicating vasoconstriction. Shortly after feeding, the ear skin temperature rose slowly to 36°C due, no doubt, to vasodilatation. There was no apparent elevation of the hypothalamic temperature, following food intake, to account for the vasodilation, since the hypothalamic temperature after feeding was never higher than before feeding when the ear was vasoconstricted. Later, when the animal fell asleep, the hypothalamic temperature fell 0.3°C to 38.35°C and no vasoconstriction occurred.

The objective for this study was to obtain a quantitative relationship between hypothalamic and skin temperature and the thermal regulatory responses of the dog. This was based on the assumption that there is a unique thermal and metabolic response for each combination of skin and hypothalamic temperature in the resting dog. The observations do not seem to support this assumption. It is not now clear to us why the hypothalamic temperature appears to be

so unrelated to the motor responses elicited by low and high environmental temperatures or by food intake. This is especially puzzling since the following results clearly indicate the contribution of the skin temperature and the hypothalamic temperature to shivering.

B. Thermal and Metabolic Responses of a Resting Dog Exposed to Neutral and Cold Environments with Thermal Clamp on Hypothalamus.

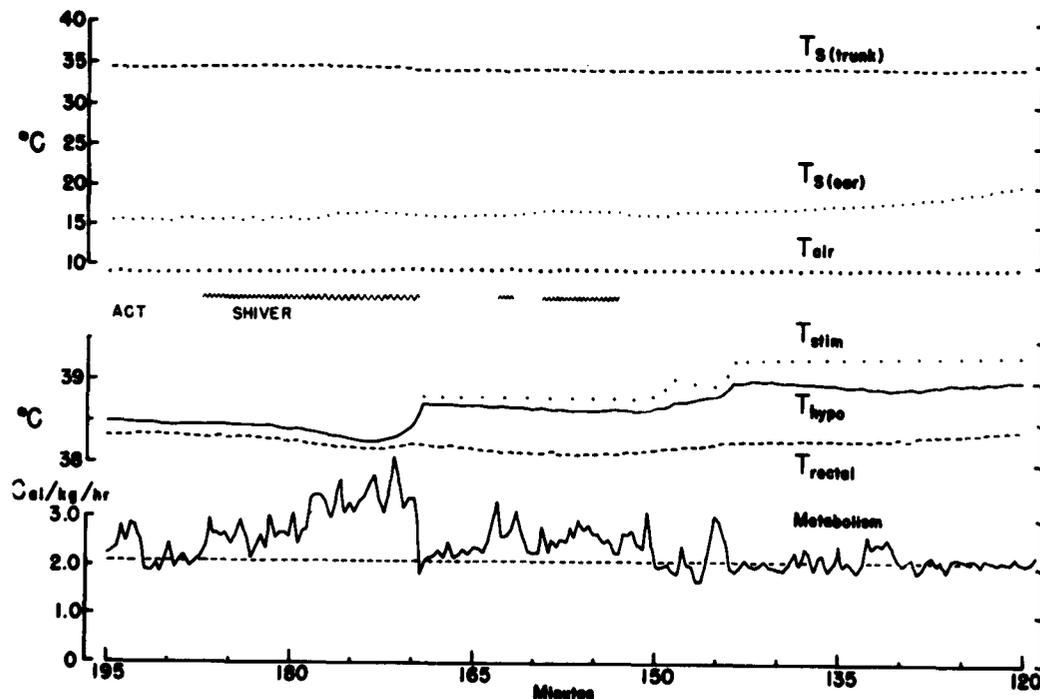


Fig. 6a Body temperatures, heat production, evaporative heat loss from mouth and temperature of thermal stimulator for the same resting, fasting dog of Figure 3 exposed to cold and hot environments.

In Figure 6a is recorded the metabolism of the same dog as used above in a 10°C environment for two hours with its hypothalamic temperature maintained at about 39°C by perfusing the thermodes with water at 39.3°C . Its metabolism was very close to the resting and basal level. At 143 minutes, the hypothalamic temperature was dropped to 38.7°C by dropping the perfusing water to 38.8°C . There was a clear increase in heat production which must be related to the low skin temperature only, since the hypothalamus was above any temperature which

would cause shivering. At 169 minutes the "thermal clamp" was removed. The hypothalamus quickly dropped to 38.3°C and shivering and metabolic rate sharply increased.

A 50 percent increase in heat production by vigorous shivering appears to result from a hypothalamic temperature of 38.3°C and low skin temperature although similar temperatures may produce no shivering, as in Figure 4a between 110 and 120 minutes. In Figure 6a the rectal temperature slowly increased to 38.5°C and the metabolic rate declined to the resting level and shivering ceased.

Figure 6b is a continuation of the run recorded in Figure 6a. Shivering and restlessness increased the heat production again as the hypothalamic temperature dropped to 38.4°C from 38.5°C. After 216 minutes the air temperature was increased from 10°C to 40°C. For a thirty minute period, the skin temperatures passively increased and vasodilation probably occurred at about 248 minutes. Vigorous panting, indicated by a respiration rate of 200 and a sharply increased evaporative heat loss, occurred at the end of the run at a hypothalamic temperature of 38.4°C, a temperature at which the dog was shivering (at 218 minutes) while the skin temperatures were still low.

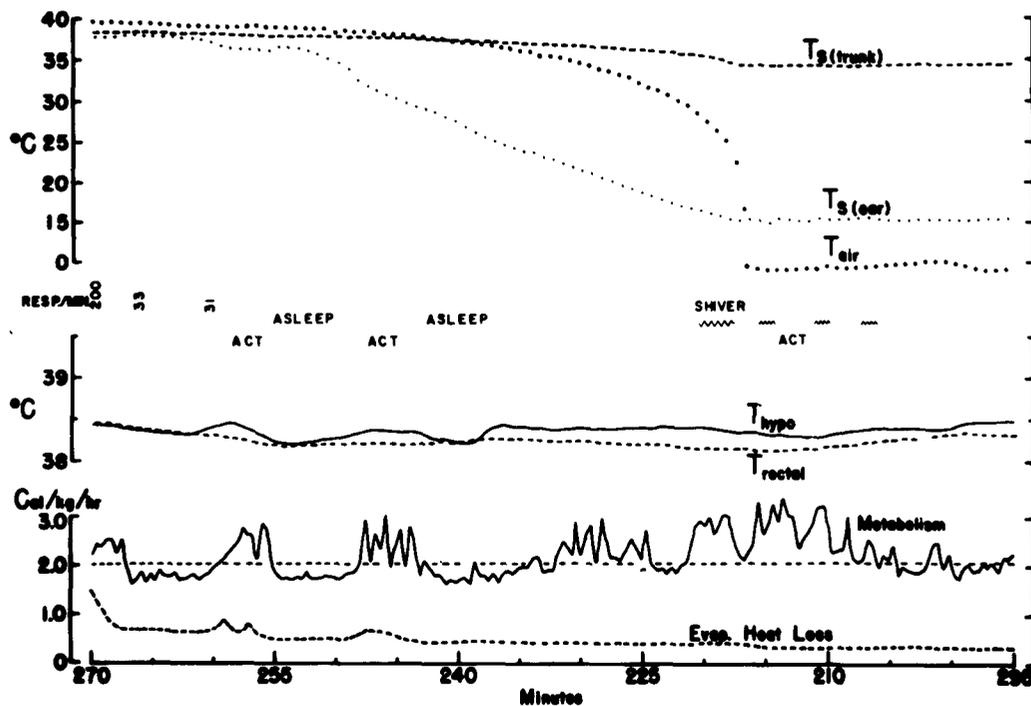


Fig. 6b Body temperatures, heat production, evaporative heat loss from mouth and temperature of thermal stimulator for the same resting, fasting dog of Figure 3 exposed to cold and hot environments.

Similar observations on another dog, a short-haired animal, less well acclimatized to cold, are seen in Figure 7. For a full hour, the dog rested quietly in a warm 30°C environment and its metabolism was basal at 1.6 Cal/kg/hr. At time 5 minutes, the thermodes were perfused with 44°C water which elevated the hypothalamic temperature to 39.3°C at the point measured. This did not affect the skin temperatures since they were already high. The metabolism was only slightly diminished and respiration rate was doubled so that the rectal temperature started to fall. Fifteen minutes later the air temperature was dropped from 30 to 14°C. Although the animal did not appear to vasoconstrict (the ear temperature was held at 30°C), the skin temperatures fell 3 to 5°C and there followed a good 50 percent increase in heat production by shivering. This shivering must have resulted entirely from extra-hypothalamic receptors, from skin receptors or core receptors stimulated by a core temperature of 37.5°C or lower. At 49 minutes the thermal clamp was shut off. The hypothalamic temperature quickly fell to 37.2°C which is about 1°C below normal for the dog and the heat production soared to 4 times basal.

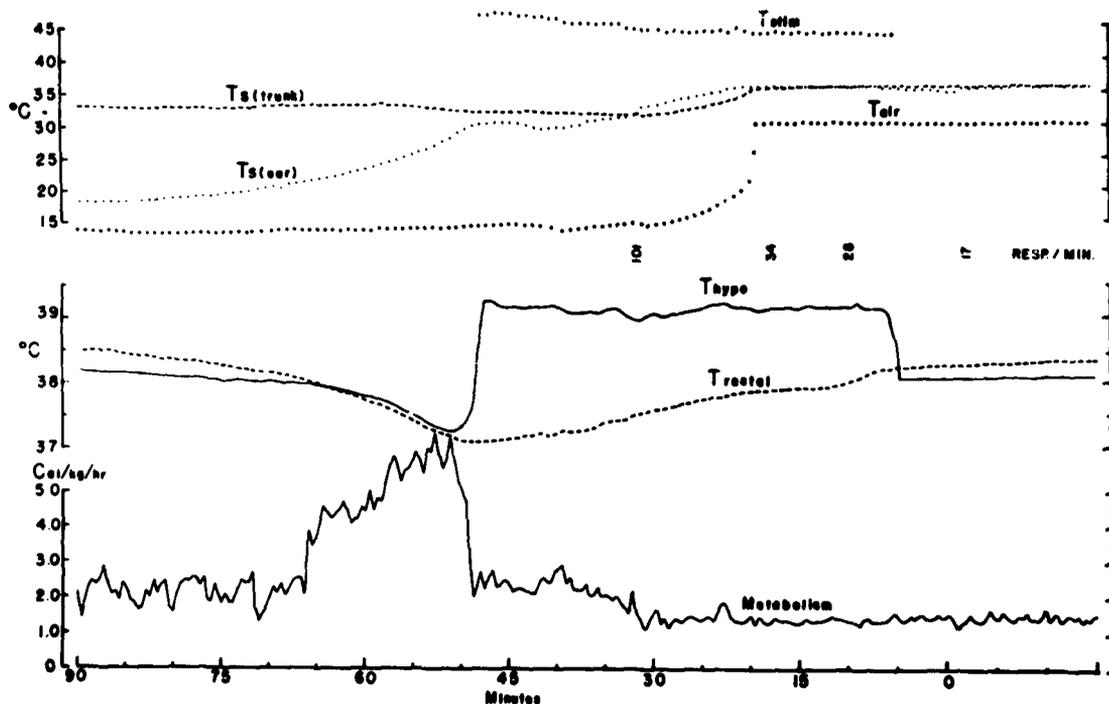


Fig. 7 Body temperatures and heat production of resting, fasting dog with thin fur exposed to neutral and cold environments.

At the same time the ear vessels vasoconstricted since the skin temperature curve turned sharply downward. As the hypothalamic temperature increased rapidly to above 38°C the heat production markedly diminished to 25 to 50 percent above the resting level.

DISCUSSION

If, in fact, there is a unique motor response for each set of internal conditions, the results obtained so far indicate that the conditions must include more than skin and hypothalamic temperatures. Other body temperatures may be involved and other influences (including feeding and food, sleep and degree of alertness, apprehension, individual personality and character, temperature to which the animal was accustomed in animal quarters, etc.) may also be involved.

The investigation has so far been limited to resting dogs in hot, neutral, and cold environments. Similar measurements of hypothalamic temperatures, rectal and skin temperatures, oxygen consumption, evaporative heat loss from the mouth must also be obtained with the exercising dog in hot, cold, and neutral environments while measuring the hypothalamic temperature and while manipulating it with the thermal stimulator.

II. Modifications of the Febrile Response to Pyrogen by Hypothalamic Heating and Cooling in the Unanesthetized Dog. H. T. Andersen, H. T. Hammel, and J. D. Hardy.

The site and mode of action of bacterial pyrogens remain a question of considerable controversy, although much work on the problem has been performed by several workers.

Fevers induced by the administration of pyrogenic substances involve both an inhibition of the mechanisms subserving heat loss, and a stimulation of those regulating heat production (ref. 6 and 7).

Liebermeister (ref. 8) suggested that fever is caused by an upward displacement of the "set point" temperature at which the centers controlling body temperature regulate. This resetting hypothesis was adopted and developed further by Du Bois (ref. 9). Chambers *et al.* (ref. 10) studied the febrile response to bacterial pyrogens in normal cats and dogs, as well as in preparations with different lesions in the central nervous system. They found that decortication, and thalamic and caudal hypothalamic lesions did not prevent the febrile response, whereas decerebrate preparations with most of the midbrain intact failed to show such an effect. Grant (ref. 11) found no evidence that pyrogenic substances influence the hypothalamic temperature regulating centers. He suggested that their action is one of interference with motor mechanisms of the lower levels of the brain stem.

Hall *et al.* (ref. 12) stated plainly that the action of bacterial pyrogens is not a resetting of the primary thermoregulatory centers of the hypothalamus, but that the thermostatic disturbances observed are elicited from a general interference of these substances on the autonomic functions controlled by the brain stem.

Thompson (ref. 7), on the other hand, showed very convincingly that dogs in which the grey matter of the posterior hypothalamus had been completely extirpated, were unable to develop a response to bacterial pyrogens.

Further information on the site of action of the bacterial pyrogens would probably be derived if their action could be counteracted or enhanced by respectively heating or cooling the thermosensitive cells of the hypothalamus during various phases of the developing fever. The results of such experiments are reported in this paper.

MATERIAL AND METHODS

Four mongrel dogs were used for the experiments. Fever was induced by intravenous administration of Piromen.*

Because dogs develop a refractoriness towards the pyrogenic action only 2 - 3 experiments were performed on each individual with 2 - 4 weeks interval between runs. The initial dose was 0.6 gamma/kg. body weight. Subsequent doses were increased by 0.2 gamma/kg. body weight in each additional experiment. These doses invariably caused a fever of roughly 1°C, and because of the moderate dosage, the side-effects, retching, vomiting and defecation were only observed in two experiments. The pyrogenic action of the bacterial polysaccharide was counteracted by heating the anterior hypothalamus with 3.7 megacycle radio frequency energy, and enhanced by cooling of the same area with circulating water. The rectal temperature was used to indicate the febrile response, and the ear temperature was measured for an indication of vasomotor activity. In the experiments in which the hypothalamus was heated, the temperature of the thermodes were recorded, and in the experiments where cooling was employed, both the stimulating and the hypothalamic temperatures were similarly measured. In these latter experiments an average skin temperature was also recorded. The details of the techniques employed have been described elsewhere (ref. 4 and 13).

The following types of experiments were carried out:

A. Heating of the hypothalamus 1) immediately after administration of pyrogen, 2) while the fever developed, and 3) when the fever condition was maximal.

* Pseudomonas polysaccharide manufactured by Travenol Laboratories, Inc., Morton Grove, Illinois, U.S.A.

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B. Cooling of the hypothalamus during the development of pyrogenic fevers so that the temperature of the hypothalamus was kept well below the rising rectal temperature.

All experiments were carried out at environmental temperatures of 27 - 28°C.

RESULTS

Normal Development of Pyrogenic Fever.

A typical development of the febrile response to intravenous administration of Piromen is shown in Figure 8. The thermode temperature is, in this experiment, the temperature of the anterior hypothalamus. The familiar two-step development of the pyrogenic fever which has been noticed by several investigators is clearly seen. The period of time which elapsed from the administration

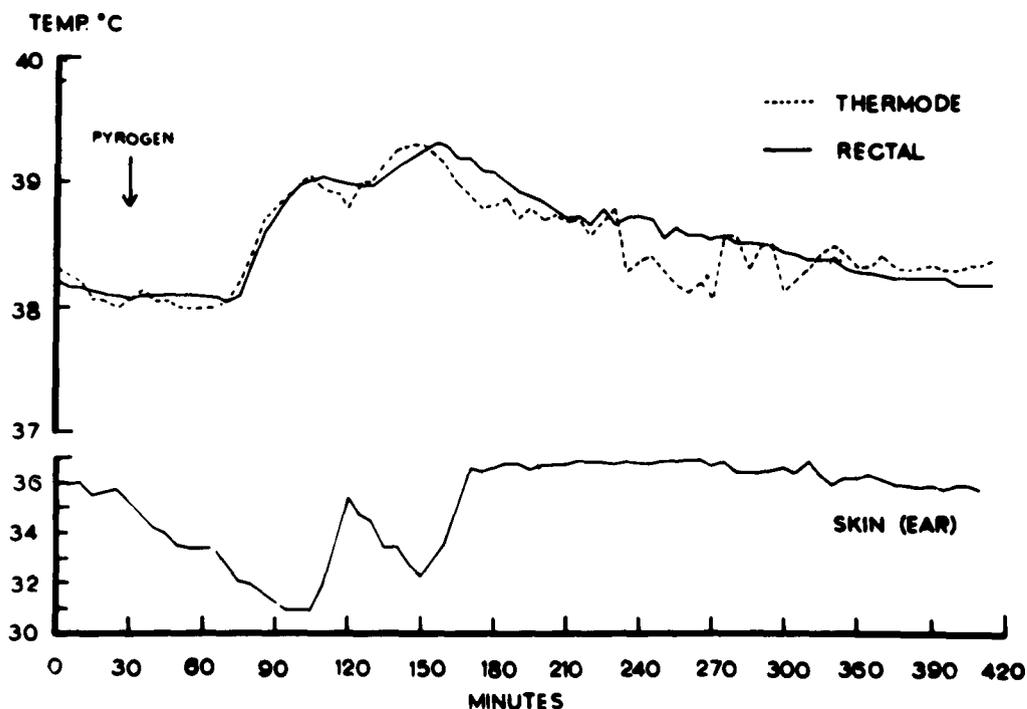


Fig. 8 Normal development of pyrogenic fever. The usual two-step rise in rectal and hypothalamic temperature is shown. Note cutaneous (ear) vasodilatation between steps.

of pyrogen until the rectal and hypothalamic temperature started rising was 35 - 45 minutes. The ear temperature mostly fell during this "latency-period." One very interesting feature of this curve is that in the normal development of

pyrogenic fever the hypothalamic temperature was always higher than the rectal, whereas during the first hour of defervescence the hypothalamic temperature was the lower of the two. In the late stages of defervescence, the hypothalamic temperature commonly started fluctuating around the rectal. Shivering was invariably exhibited during the fever development, and panting likewise during defervescence.

Hypothalamic Heating Immediately After Administration of Pvrogen.

In order to inhibit the development of fever after the administration of pyrogen, the anterior hypothalamus was heated as soon as Piromen had been injected. The result is presented in Figure 9. The ear temperature rose in response to the heating, and the rectal temperature fell slowly. After a normal latency of 45 minutes, a period followed during which the ear temperature fell throughout, the animal exhibited a small rise in the rectal temperature, but only enough to bring it up to 0.2°C above that of the period before pyrogen

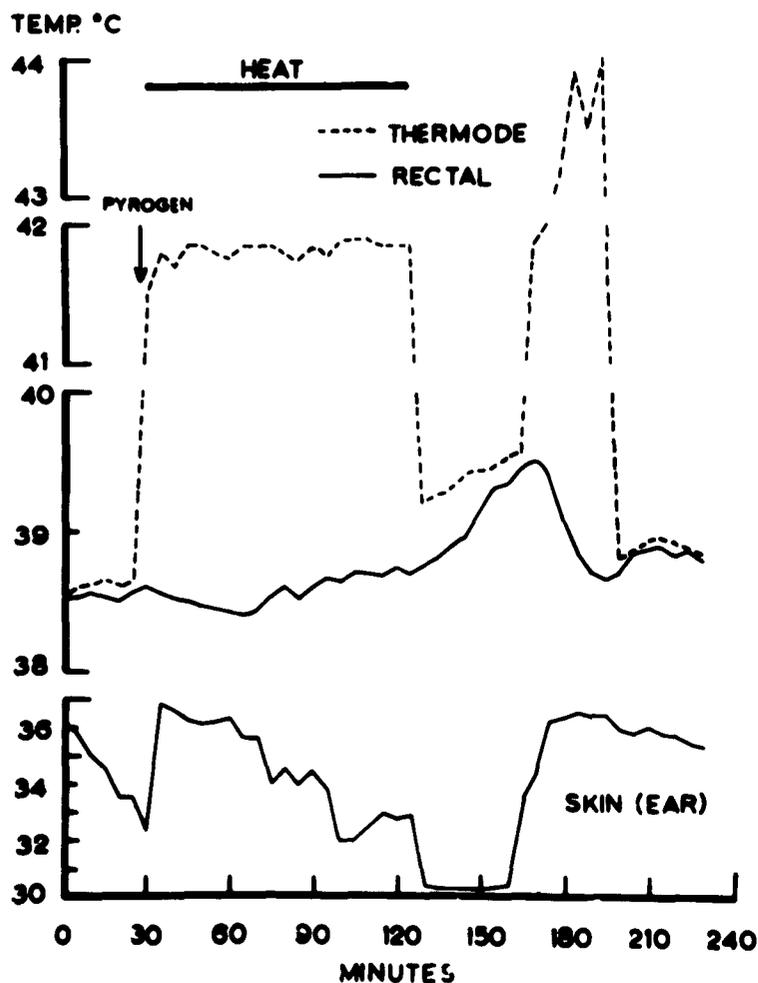
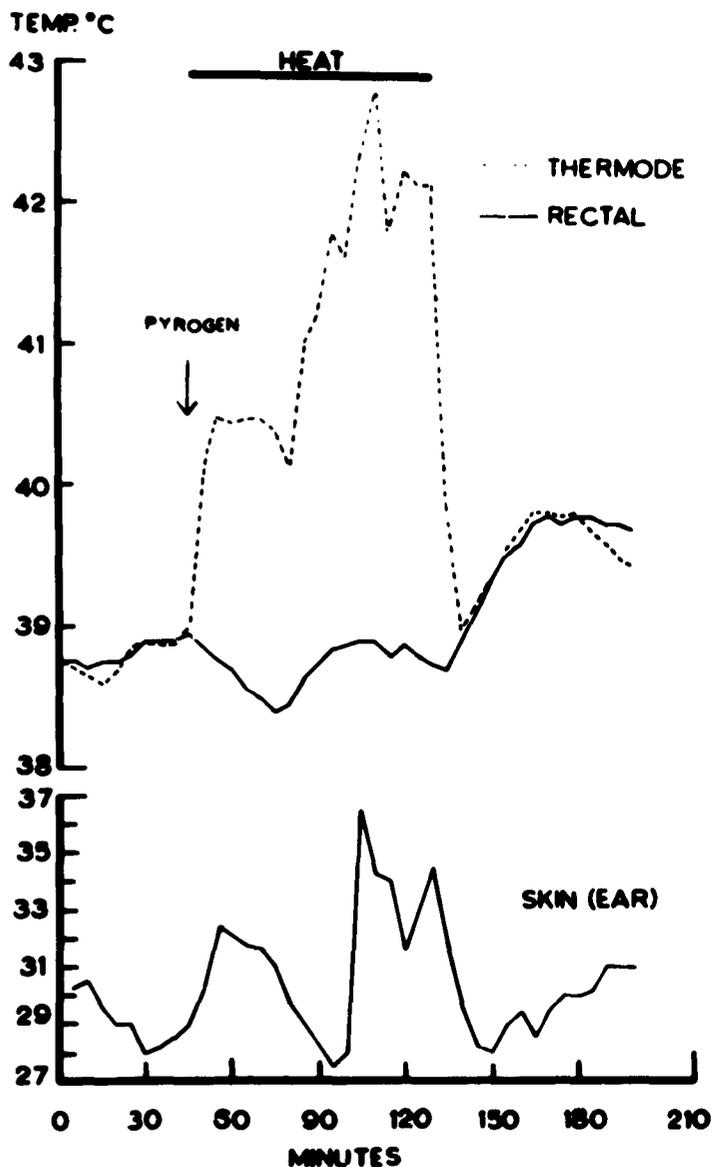


Fig. 9 Inhibition of the febrile response to "Piromen" by heating the stimulating thermodes to 41.8°C after the administration of the pyrogen. The normal response followed immediately after discontinuing the thermal stimulus.

was administered. During the continued heating of the hypothalamus, this level of rectal temperature was maintained without significant changes for 45 minutes. When the heat stimulation of the hypothalamus was cut off, the ear temperature fell abruptly. The rectal temperature rose rapidly 1.0°C above the resting level. By heating the anterior hypothalamus to a higher temperature than before it was possible to induce cutaneous vasodilation as seen from the ear temperature, and a precipitous fall in the rectal temperature. When the heating was stopped, the rectal temperature increased by 0.3°C and then levelled off.



When the heating was stopped, the rectal temperature increased by 0.3°C and then levelled off.

Fig. 10 Inhibition of pyrogenic fever during its development due to hypothalamic heating. The febrile response was obtained upon discontinuation of the thermal stimulus.

Inhibition of a Developing Fever by Hypothalamic Heating.

Another experiment is shown in Figure 10. Pyrogen was given, and the thermode temperature was kept only 1.5°C above the rectal temperature. Due

to this slight stimulation, the ear temperature indicated vasodilation, and the rectal temperature fell roughly 0.6°C . 30 minutes after the injection, the ear temperature started decreasing, the fever developed accompanied by shivering, and the hypothalamic temperature fell in spite of unchanged stimulation. The rectal temperature increased rapidly. By increasing the stimulating temperature in the thermode to $42 - 43^{\circ}\text{C}$ it was possible to inhibit the developing fever and lower the rectal temperature due to vasodilation (see ear temperature) and panting. Stoppage of the heat supply to the hypothalamus brought about vasoconstriction, vigorous shivering and an abrupt rise in rectal temperature to 1.2°C above the resting.

Effect of Hypothalamic Heating on Fully Developed Pyrogenic Fever.

Figure 11 shows an experiment in which the fever was allowed to develop normally. When a stage had been reached at which the rectal temperature levelled off after having increased 1.0°C above normal, the anterior hypothalamus was heated as shown. The responses elicited were strong cutaneous vasodilation and a marked fall in rectal temperature of 0.6°C . Removal of the stimulus caused vasoconstriction, shivering, and a second rise in rectal temperature almost to the same level as the first. The same sequence of events followed repeated stimulation, and a third rise in rectal temperature was

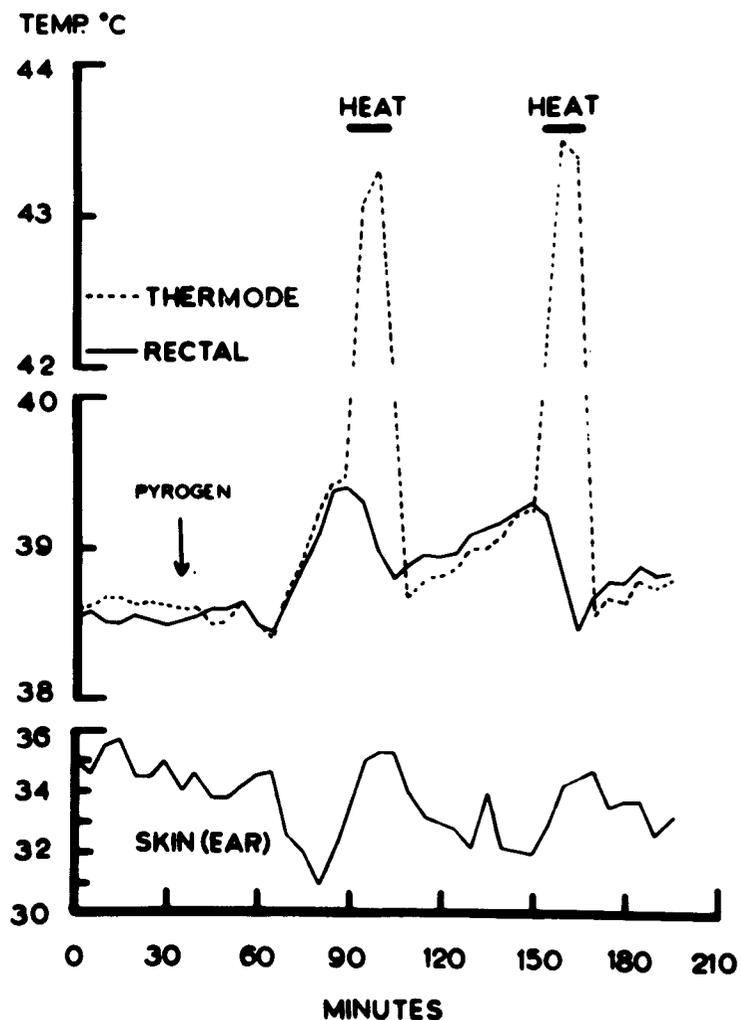


Fig. 11 Hypothalamic heating applied in the case of fully developed pyrogenic fever. The thermal responses elicited were very similar to those obtained at normal body temperature.

produced after the heating had been discontinued. This shows that the pyrogenic substance was exerting its effect throughout the experiment.

Hypothalamic Cooling and Pyrogenic Fever Development.

In the experiments in which the anterior hypothalamus was cooled after the pyrogen had been given, a summation of these two stresses was obtained. The result, an elevation of the rectal temperature well above the level corresponding to the pyrogen alone, is demonstrated in Figure 12. As soon as the cooling was stopped, the ear temperature increased 7°C, and the animal started panting. The average skin temperature also rose conspicuously. This situation, however, lasted for only 10 - 12 minutes, during which the rectal temperature fell from 40.4°C to 40.0°C. The rectal temperature levelled off at this point and remained almost constant for 35 - 40 minutes before the onset of defervescence. The hypothalamic temperature also rose during the stages in which the fever developed. This was inevitable in order that the temperature of the circulating water should be held within relatively physiological limits (38 - 33°C). An experiment was performed where the hypothalamic temperature was kept almost constant, but to obtain this constancy the stimulating temperature had to be lowered to 26.6°C. The findings in this latter experiment were essentially the same as those reported in Figure 12, except that a peak of 41.1°C in rectal temperature was reached. After abolishing the cold stimulation, the rectal temperature due to the pyrogen alone was found to be 40.6°C.

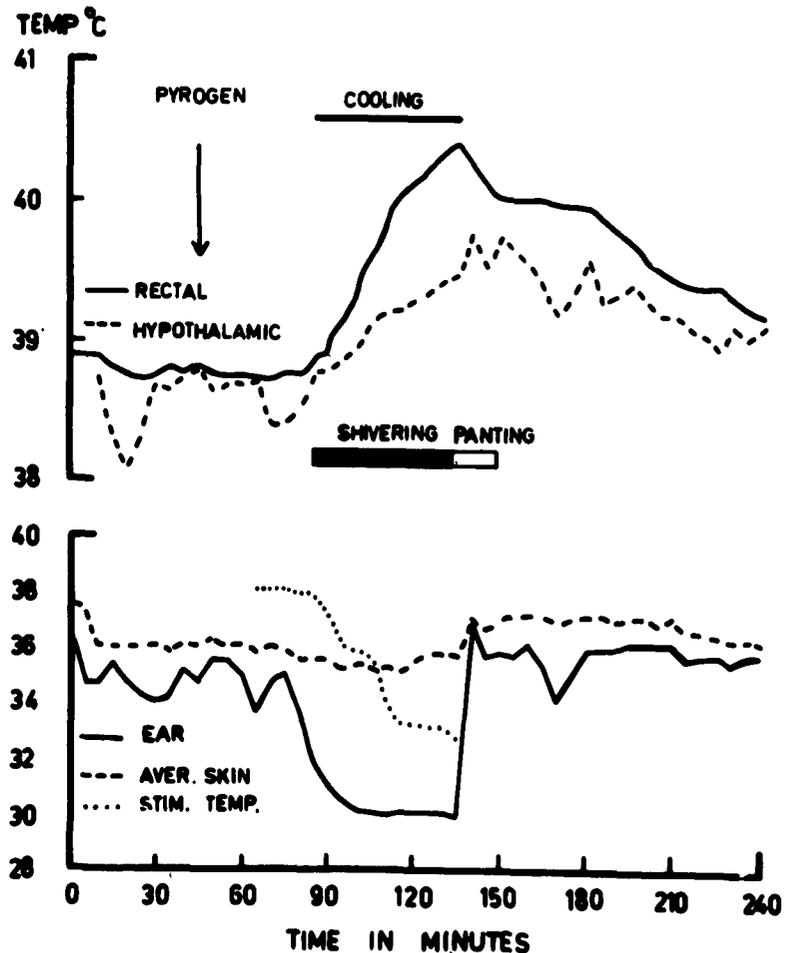


Fig. 12 The additive effect of injected pyrogen and hypothalamic cooling. A "hyperfever" was produced.

DISCUSSION

The clear-cut summative effects of hypothalamic heating and cooling with the febrile effects of an injected pyrogen as shown in this paper are in marked contrast to the complete lack of such summation of external heating or cooling and pyrogenic action shown in man by Park and Palmes and in the dog by Thompson. The summation, however, closely parallels the observations of Fox and Macpherson (ref. 14) who observed a young man who was in a group being studied during a routine of exercise over a period of some weeks and who developed an infection with a fever during the course of the experiment. Despite the fever, he insisted that he was fit to continue in the experiment and his pattern of temperature response to the exercise was measured before, during, and after recovery from his illness. During the febrile period his response was identical to that in the non-febrile periods except that the temperature pattern was displaced to a higher level by a fixed amount, i. e. the elevation above its usual resting level. From this they concluded that "the body regulated its temperature about a new level, the exact value of which depended upon the existing fever level." Thus, the temperature regulation during a pyrogenic fever is well established and the level of regulation is not appreciably affected by external heating or cooling but is markedly affected by general internal heating, or local heating or cooling of the anterior hypothalamus.

These observations support the concept that the action of the pyrogen in causing fever, even though this action be a secondary one as indicated by the work of Bennett and Beeson (ref. 15, 16 and 17), is on the cells of the anterior hypothalamus, i. e. on the thermally sensitive cells of this region which are associated with temperature regulation. Thus, if the animal has been given a pyrogen and as a result begins to react as if its body temperature had been lowered, these reactions can be abolished by heating to febrile levels the small volume of hypothalamic tissue previously described. However, pyrogenic substances act on many other structures, and perhaps more directly, than they do on the thermoregulatory cells of the anterior hypothalamus and the present experiments shed no light on such action. Gerbrandy et al., (ref. 18 and 19) and Snell (ref. 20) feel that purified pyrogens act principally on the central nervous system and the vomiting and defecation often seen after administering pyrogens may be evidences of these actions. However, it cannot be said from the evidence now available that any of the actions of pyrogens is completely understood.

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